REMARKS

Claims 1-17 were pending. Claims 3-8 have been withdrawn as directed to a non-elected invention. Claims 1 and 3 have been amended. No new matter has been entered.

Objections

The disclosure stands objected to because of the use of trademarks in the specification. Applicants have amended the specification to capitalize trademarks and provide generic terminology in the first instance of the use of the trademark. If there are other trademarks where no generic terminology is included Applicants respectfully request that the Office point them out.

The disclosure stands objected to because of a typographical error. Applicants have amended the specification to correct the typographical error.

In view of the foregoing, Applicants respectfully request that the objections to the specification be withdrawn.

Claim 2 stands objected to under 37 C.F.R. § 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of claim 1. Applicants have canceled claim 2 rendering this objection moot.

In view of the foregoing, Applicants respectfully request that the objection to the claims be withdrawn.

Rejections under 35 U.S.C. 112, second paragraph

Claims 1-4, 6-11, 13-15 and 37-47 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully disagree.

According to the Office, claims 1-4, 6-11, 13-15, and 37-47 are allegedly indefinite because

> Claim 1 is drawn to a method for detecting the presence of a disseminated epithelial cell marker, however, the final step is for detecting the presence of mRNA. The claims do not set forth the relationship between detecting the presence of mRNA and detecting the presence of a disseminated epithelial cell marker.

> Therefore, it is not clear as to whether the claims are intended to be limited to a method of detecting the presence of a disseminated epithelial cell marker or detecting the presence of mRNA.

(Office Action, page 3). Applicants respectfully disagree, but in order to further prosecution claim 1 has been amended to further clarify the it is a method of detecting the presence of a disseminated epithelial cell marker.

The Office also alleges that claims 1-4, 6-11, 13-15 and 37-47 are indefinite for the usage of the term "disseminated epithelial cell marker" because it is not clear as to what is meant by this recitation. The Office also alleges that "the specification does not specify which epithelial cell markers are considered to be 'disseminated' or which epithelial cell markers are capable of being 'disseminated'". (Specification, page 4). Applicants respectfully disagree.

The term "disseminated" as it refers to a cell means "a cell that is found in a location in the body that is different from its site of origin or normal location in the body." (Specification, as-filed, p. 11, line 31 – p.12, line 2). The term "disseminated cell marker" refers to "a gene product associated with a particular cell or tissue type that may serve as an indication that a cell has become disseminated from its site of origin or normal location in the body." (Specification, as-filed, p12, lines 10-12) One of skill in the art would clearly understand the meaning of this term after reading the claims and the specification. The skilled artisan would understand the term "epithelial" and therefore, would understand that, by definition, a "disseminated epithelial cell marker" refers to any gene product that is associated with epithelial cells that has become dispersed from its site of origin or normal location in the body. The skilled artisan would understand that any epithelial gene marker is capable of being disseminated and it is through the present invention that the presence of such markers is detected.

Accordingly, the claims are definite because the skilled artisan would clearly understand the meaning of the claims. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 4 and 40 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Office alleges that the claims

contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, has possession of the claimed invention. The Office alleges that the claims contain new matter. Applicants respectfully disagree.

Although all the markers listed in claims 4 and 40 are not specifically identified in the specification as epithelial cell markers, the markers themselves are inherently epithelial cell markers. One of ordinary skill in the art would know that the listed markers are epithelial cell markers. In support of Applicants assertion that the marker are known to be epithelial cell markers Applicants provide herewith an executed copy of a declaration of Dr. Scott A. Waldman pursuant to 37 CFR § 1.132. The declaration clearly states that "The markers that are listed in Claims 4 and 40 are known to be epithelial cell markers. Furthermore, one of ordinary skill in the art would know that the markers listed in Claims 4 and 40 are epithelial cell markers." (Declaration, p.1)

Accordingly, claims 4 and 40 do not introduce new matter. In view of the foregoing, Applicants respectfully request that the rejection be withdrawn.

Claims 1-4, 6-11, 13-15 and 37-47 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office further alleges that the genus encompassed by the claims

> comprises the class of compounds (mRNAs) that share a function (encoding a disseminated epithelial cell marker, wherein the marker is a differentiation-specific antigen). However, the specification does not specify a common structure of this class of mRNAs. That is, while the members of the genus encompassed by the claims...share a function, they do not share a structure that is similar. Each mRNA encompassed by the genus will have different structure, absent any disclosed structural similarities provided by the specification. That is, even assuming, the mRNAs encompassed by the genus are functionally similar, they are <u>not</u> structurally similar, and therefore, the functional description of the

> mRNAs does not provide adequate written description to the plurality of other structurally distinct mRNAs that are encompassed by the claimed invention.

(Office Action, page 6). Applicants respectfully disagree.

The M.P.E.P. states,

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see i)(A), above), reduction to drawings (see i)(B), above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

(M.P.E.P.§ 2163).

The Office alleges that Applicants have only described "eight epithelial cell markers". (Office Action, page 7). However, Applicants have described over 3 times that number (see, for example, the 26 markers listed in claim 4). Therefore, Applicants have described a representative number of species of the genus.

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

(M.P.E.P § 2163). Although, the mRNA sequence of each marker is different, each sequence is a nucleic acid molecule. Applicants have described a variety of the species that "reflect the variation within the genus." The Office further alleges that the "specification does not describe which mRNA are specific for a particular tissue-specific marker." (Office Action, page 7). Applicants are not required to describe every member of a genus as the Office alleges. Rather, the skilled artisan would know other tissue-markers that can be used as disseminated epithelial markers. The present invention provides a method for eliminating illegitimate transcription by eliminating CD34+ cells and then using the remaining population of cells to detect the mRNA of a disseminated epithelial marker. The exact marker that is used is not necessary to show

possession of the invention at the time the application was filed. Applicants have provided examples of disseminated epithelial markers, but the skilled artisans can use any disseminated epithelial marker of their choosing. As discussed above, the specification defines a disseminated marker as referring to "a gene product associated with a particular cell or tissue type that may serve as an indication that a cell has become disseminated from its site of origin or normal location in the body." Thus, Applicants were clearly in possession of the genus at the time the application was filed.

Claims 1-4, 6-11, 13-15, and 37-47 stand rejected under 35 U.S.C. § 112, first paragraph, because allegedly the specification while

> being enabling for a method of detecting the presence of an CD34+ cells, comprising the steps of a)eliminating CD34+ cells from the sample; and b) detecting the presence of said epithelial cell marker, wherein said epithelial cell marker is selected from the group consisting of CEA, PSA, PSM, CK-19, MUC-1 and GA733.2, does not reasonably provide enablement for methods of detecting the presence of disseminated epithelial cell marker in a sample comprising the steps of a) eliminating CD34+ cells from the sample; and b) detecting the presence of mRNA that encodes the marker, wherein the marker is a differentiation specific antigen.

(Office Action, page 8). The Office also alleges that specification only teaches eight epithelial cell markers and that these can be used as disseminated markers. The Office further alleges that "the specification does not provide any guidance on any other types of mRNA which encode disseminated epithelial cell markers... nor does the specification provide any guidance on the reduction of illegitimate transcription of any other disseminated epithelial cell markers." (Office Action, page 10). Applicants respectfully disagree.

"A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, *e.g.*, *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)." (M.P.E.P § 2163). The Office has failed to provide any "adequate reasons" as to why a person skilled in the art would not use the genus as a whole without undue experimentation. The Office alleges that one of skill in the art would have determine mRNAs that encode other "disseminated epithelial cell markers" and that it would be trial and error, with "little to no starting point". However, the Office has

failed to provide any evidence demonstrating that one of skill in the art would need to practice undue experimentation. The Office lists several allegations but has not supported any of its allegations with any sound scientific reasoning other than general statements like when the Office states "the results...are unpredictable." (Office Action, page 11). Conclusory statements are insufficient to support an allegation that claims are not enabled. Accordingly, without such evidence the rejection should be withdrawn.

The M.P.E.P. also states:

> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. § 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)."

(M.P.E.P § 2163). The M.P.E.P. also states that,

> Proof of enablement will be required for other members of the claimed genus ***only*** where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

(M.P.E.P § 2163, emphasis added). Applicants have provided at least one method for using the claimed invention that "bears a reasonable correlation to the entire scope of the claim". The Office has not advanced "adequate reasons" as to why the members of the genus that are described in the specification and claims do not bear a reasonable correlation to the entire scope of the claims.

If the Office maintains the enablement rejection with only written allegations that appear to be only based on the knowledge of the Examiner, Applicants respectfully request that the Examiner submit an affidavit as to why the present application is not enabled in view of the absence of other scientific evidence (*i.e.* scientific publications).

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. § 112 be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-4, 7-11, and 13 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Zippelius *et al.* (Journal of Clinical Oncology (1997) 15(7):2701-2708, hereinafter

"Zippelius"). The Office alleges that Zippelius discuses methods of detecting the presence of a disseminated epithelial cell marker comprising the steps of: eliminating CD34+ cells from the sample and detecting the presence of mRNA that encodes the marker, wherein the marker is a differentiation-specific antigen. The Office states

> It is noted that the removal of mononuclear cells before RT-PCR meets the limitation of "eliminating CD34+ cells", since mononuclear cells from bone marrow will contain CD34+ cells. Furthermore, the claims are drawn to "eliminating CD34+ cells", which can be interpreted as only eliminating a fraction of mononuclear cells.

(Office Action, page 13-14). Applicants respectfully disagree.

For a reference to anticipate a claim each and every element as set forth in the claim must be found either expressly or inherently described in a single prior art reference. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984).

Claims 1-4, 7-11, and 13 are not anticipated by Zippelius because the reference does not describe either expressly or inherently every element of the claims. Claim 1 states

> A method of detecting the presence of a disseminated epithelial cell marker in a sample comprising the steps of
>
> a) eliminating CD34+ cells from the sample; and
>
> b) detecting the presence of mRNA that encodes the marker; wherein the marker is a differentiation specific antigen;
>
> wherein said detection of said mRNA indicates the presence of a disseminated epithelial cell marker.

The Office alleges that Zippelius removes mononuclear cells before performing RT-PCR. However, Applicants respectfully assert that the Office has misinterpreted the reference. Zippelius states

> BM [bone marrow] was aspirated...The volumes aspirated varied from 6 to 10 mL which yielded between $6X10^6$ to $5X10^7$ mononuclear cells (MNC). ***MNC were isolated by density-gradient centrifugation...A fraction of these cells were removed for RT-PCR analyses***, and the remaining cells were deposited onto glass slides by cytocentrifugation at 150 x g for 8 minutes.

(Zippelius, p. 2702, left column, lines 13-21, emphasis added). Zippelius has not ***eliminated*** CD34+ cells, rather Zippelius enriched the sample for the mononuclear cells and performed RT-PCR on the mononuclear cells. Accordingly Zippelius fails to anticipate claim 1. Zippelius also fails to anticipate claims 2-4, 7-11, and 13 because these claims all depend from claim 1, which is not anticipated by Zippelius.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102 be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-4, 7-11, 13, 37-40, and 42-45 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ts'o et al (U.S. Patent No. 5,962,237), in view of Palsson, B. (U.S. Patent No. 5,874,266). The Office alleges that Ts'o discusses methods of isolating and enriching rare cells from body fluids by negative selection of non-tumor cells such as white blood cells from the CD family. However, as the Office points out, Ts'o fails to teach the removal of CD34+ cells. The Office alleges that Palsson discusses that eliminating CD34+ cells from tumor cells is advantageous to ensure isolation of only the tumor cells and that negative CD34+ selection can be used in conjunction with detection of epithelial cell markers. The Office alleges that

> in view of the teachings of Palsson, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ts'o so as to have eliminated CD34+ cells from rare cancer cells. One of ordinary skill in the art would have been motivated to modify the method of Ts'o to have eliminated CD34+ cells, in order to have achieved the benefit of providing a more effective means of detecting epithelial cell markers by reducing contamination caused by the CD34+ cells.

(Office Action, page 15). Applicants respectfully disagree.

The Ts'o reference

The Ts'o reference discusses a "Method of Enriching Rare Cells". However, the Ts'o reference fails to discuss the elimination of CD34+ cells. One of ordinary skill in the art would not have been motivated to remove CD34+ cells. The Ts'o reference explicitly discusses using antibodies against many CD proteins, but does not refer to CD34. The Ts'o reference

specifically discusses using antibodies against each of CD2, CD3, CD4, CD5, CD7, CD8, CD11a, CD11b, CD11c, CD14, CD15, CD16, CD19, CD20, CD28, CD36, CD42a, CD 43, CD44, CD45, CD45R, CD45RA, CD45RB, CD45RO, CD57, and CD61. In particular, the Ts'o reference states that "Antibodies targeted to human CD45, CD3, CD19, CD14, and CD36 are preferred." (Ts'o, Col. 12, lines 4-5). The Ts'o reference also has 14 examples, which only use antibodies that are targeted to human CD45, CD3, CD19, CD14, and/or CD36. The Ts'o reference does not motivate one of skill in the art to use antibodies directed against CD34 to remove CD34+ cells. Therefore, the Ts'o reference fails to teach all the elements of the invention.

The Palsson reference

The Palsson reference discusses a "Targeted System for Removing Tumor cells from Cell Populations". The Palsson reference states, "In particular, this invention relates to methods for specifically labeling and thereafter ***individually killing tumor cells*** with a focused high-energy beam such as a laser beam." (Palsson, Col. 1, lines 8-11, emphasis added). Palsson also describes the invention as providing "a targeted method of individually identifying and ***destroying contaminating tumor*** cells in a cell population." (*Id.* Col. 1, lines 42-45, emphasis added). Therefore, one of ordinary skill in the art would read the Palsson reference as teaching methods to remove and kill tumor cells.

One of ordinary skill in the art would not be motivated to apply the teachings of Palsson in methods to *detect* (not destroy) tumor cells. Palsson teaches a method of killing tumor cells and ***away*** from detection methods that would require the tumor cells be present. One of skill in the art would not have been motivated to modify the Palsson reference to obtain the present invention because to detect a disseminated epithelial marker, the skilled artisan would need a tumor cell to be present, not destroy it as the Palsson reference teaches. Furthermore, although the Palsson reference discusses isolating CD34+ cells along with several other methods that have been used to isolate normal cells from tumor cells, Palsson states "Unfortunately, the whole population tumor purging methods...do not kill or remove all ***contaminating tumor cells*** from the harvested stem cell population." (*Id.*, Column 3, lines 21-24, emphasis added).

Clearly, in his desire to kill tumor cells, Palsson teaches away from the Ts'o reference and the present invention. Palsson teaches away from eliminating CD34+ to detect a disseminated epithelial marker that are produced by tumor cells because Palsson describes the purpose of the reference is to eliminate the "contaminating tumor cells". A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). There is no motivation to combine the Ts'o and Palsson references because the teachings of the references are completely opposite of one another.

However, even if there were motivation to combine Ts'o and Palsson, one of ordinary skill in the art would not obtain the claimed invention when the references are thus combined and taken as a whole. As discussed above claim 1 recites:

> A method of detecting the presence of a disseminated epithelial cell marker in a sample comprising the steps of
>
> a) eliminating CD34+ cells from the sample; and
>
> b) detecting the presence of mRNA that encodes the marker; wherein the marker is a differentiation specific antigen;
>
> wherein said detection of said mRNA indicates the presence of a disseminated epithelial cell marker.

The claimed invention comprises eliminating CD34+ cells from a sample and then detecting the presence of mRNA that encodes a disseminated epithelial cell marker.

The references must be taken as a whole when ascertaining what they teach. Taken as a whole, the Palsson reference teaches how to destroy tumor cells not isolate them. Taken as a whole, the Ts'o reference teaches a method that does not eliminate CD34+ cells, but teaches how to isolate rare cells using antibodies against various proteins other than CD34. Thus, when the references are taken as a whole and combined, the result is a process that isolates rare cells (Ts'o reference) and then destroys them (Palsson reference). Therefore, a combination of the Ts'o reference and the Palsson reference would create an invention that destroys tumor cells, which is exactly opposite of the present invention.

Accordingly, the rejection for alleged obviousness is still improper, even if there were some motivation to combine the teachings of the cited references (and Applicants maintain that there is no such motivation), because a person of ordinary skill seeking to combine these references at the time of Applicants' invention would not have been led to any claimed subject matter. The Office is respectfully reminded that when assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a ***whole*** without undue emphasis on those features that would support a finding of obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art). Consideration of the cited references as a whole for what they each fairly suggest, demonstrates that a person of ordinary skill seeking to combine them would not have produced any claimed invention.

The Palsson reference and the Ts'o reference also fail to render the present invention obvious because the references do not motivate one of skill in the art to remove CD34+ cells to remove the high false positive rate that was associated with detection methods prior to the present invention. The present specification sates, "The high false positive rates appear to arise from illegitimate transcription of epithelial cell markers." (Specification, p.1, lines 24-25). Medical tests that have a high incidence of false positives can increase the cost of medical care as well as negatively impact an individual that is believed to be positive for a condition when in fact that individual is not. As the specification states:

> there is a need for methods of reducing the background signals caused by illegitimate transcription of cell markers used for the detection of cells that have migrated from their normal location in the body, including metastatic cancer cells. In particular there is a need to improve the accuracy and to decrease false-positive signals in highly sensitive, mRNA detection assays.

(Specification, page 5, lines 14-19). The present invention solved the problem of false positives by identifying the main culprit, CD34+ cells. It is well settled that where the claimed invention solves a problem (false positives), the discovery of the source of the problem (CD34+ cells) and its solution (eliminating CD34+ cells) are considered to be part of the "invention as a whole"

under 35 U.S.C. §103. *In re Kaslow*, 707 F.2d 1366, 217 U.S.P.Q. 1089 (Fed. Cir. 1983); *In re Nomiya*, 509 F.2d 566, 184 U.S.P.Q. 607 (C.C.P.A. 1975); and *In re Sponnoble*, 405 F.2d 578, 160 U.S.P.Q. 237 (C.C.P.A. 1979). Neither the Ts'o reference nor the Palsson reference, alone or in combination, claimed to solve the problem of false positives or identified a solution, and therefore, do not render any invention obvious.

Claims 6 and 41 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ts'o *et al.* (U.S. Patent No. 5,962,237), in view of Palsson, B. (U.S. Patent No. 5,874,266) and in further view of Elliot (U.S. Patent No. 5,885,574). Applicants respectfully disagree.

Claims 14-15 and 46-47 stand rejected under 35 U.S.C. § 103 (a) as allegedly unpatentable over Ts'o *et al.* (U.S. Patent No. 5,962,237), in view of Palsson, B. (U.S. Patent No. 5,874,266) and in further view of Waldman *et al.* (Cancer Epidemiology, Biomarkers & Prevention (1998) 1:505-514). Applicants respectfully disagree.

As discussed above, one of ordinary skill in the art would not have been motivated to combine the Ts'o reference and the Palsson reference. Furthermore, even if the references were combined, the result would not yield Applicants' invention for the reasons discussed above.

Elliot and Waldman et al. do not overcome the deficiencies of Ts'o and Palsson. Thus, claims 6, 14-15, 41, and 46-47 are also not obvious over the asserted combination of references.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

Conclusion

The examination of these claims and passage to allowance are respectfully requested. An early Notice of Allowance is therefore earnestly solicited.

Respectfully submitted,

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